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CHAPTER 24

The HPA-axis and immune function in burnout

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Abstract: Burnout results from chronic work stress. Its complaints may be related to HPA-axis disturbances or changes in immune function. In our studies the salivary cortisol awakening response, day-curve, and the suppressed level after dexamethasone intake were not different in a burned-out group compared to a control group. Nor was there a change in cortisol after a treatment period. Higher levels of DHEAS and the monocyte released anti-inflammatory cytokine IL-10 were observed, however T-cell stimulated and dexamethasone inhibited cytokine release were not affected. The increased IL-10 level may be related to an increased sensitivity for infections.

Keywords: burnout; chronic stress; cortisol; cytokines; dexamethasone suppression test; DHEAS; follow-up

Introduction

Burnout is the ultimate outcome of a chronic process in which work stress is supposed to play a decisive role. People with burnout feel extremely fatigued, have become alienated from their work, experience reduced professional competence, and report a whole range of complaints such as depressed mood, increased irritability, inability to relax, disrupted sleep, somatic complaints such as aching muscles, headaches, gastro-intestinal problems, and concentration and memory problems (Maslach et al., 2001). When we assume that burnout is a stress-related syndrome, one may expect to find a disturbance in hypothalamus pituitary adrenal (HPA)-axis functioning. Inadequate glucocorticoid signaling has been suggested for other stress-related syndromes like post-traumatic stress disorder (PTSD), chronic fatigue syndrome (CFS), and major depression disorder (MDD). Reviewing the literature on burnout and related stress-syndromes has led to the hypothesis that the fatigue symptoms in burnout are related to a state of hypocortisolism, and increased feedback sensitivity of the HPA-axis (Heim et al., 2000). On the other hand, the depressive symptoms would suggest a hypercortisolemic state, and a relative non-suppression in response to dexamethasone (DEX) (Raison and Miller, 2003). Assuming a disturbance of the HPA-axis in burnout, we expected a reduction in burnout complaints to be related to a recovery of this disturbance. A longitudinal study was set up to correlate changes in complaints with changes in salivary cortisol parameters.

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Glucocorticoids play a decisive role in immune functioning. Cortisol inhibits pro-inflammatory cytokine release, e.g., TNF-α, IFN-γ, interleukin (IL)-6 and IL-1, and stimulates anti-inflammatory IL-10 and IL-4 release (Elenkov and Chrousos, 2002). Chronic psychosocial stress has been related to impaired immune functioning leading to physical illness. This process may be mediated by glucocorticoids through affecting the balance between pro- and anti-inflammatory cytokines (Kiecolt-Glaser et al., 2002).

Results

The major finding of our study was the absence of a disturbance in salivary cortisol parameters in burnout. A burnout group ($n = 74$) was compared to a healthy control group ($n = 38$). The burnout persons were on sick leave, and had received a clinical diagnosis for work-related neurasthenia according to International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria. Primary Diagnostic and Statistical Manual of Mental Disorders Edition IV (DSM-IV) disorders such as MDD or anxiety disorder were excluded. The cortisol awakening response (CAR) was measured on 2 days at 0, 15, and 30 min after awakening, and at noon, 18:00 h and 22:30 h to assess the diurnal cortisol course. A low-dose (0.5 mg) DEX was taken to test the feedback sensitivity of the HPA-axis. The suppressed cortisol level after DEX intake was measured at 0, 15, and 30 min after awakening. The cortisol CAR, day-curve and suppressed DEX level were not different between the burnout and control group (Mommersteeg et al., 2006a–c) (Fig. 1). Cortisol was not related to fatigue or depression complaints within the burnout group, thus showing no indication of an opposing hypo- or hyperfunction of the HPA-axis, potentially masking the effect in burnout.

Because there is considerable variation in cortisol levels between and within persons, it is quite well possible that within a group burnout persons the reduction of the burnout complaints will covary with the cortisol parameters after a treatment and a follow-up period. This possibility was studied in the longitudinal part of the previous study (Mommersteeg et al., 2006). Burnout complaints were significantly reduced after a treatment period, without a further reduction at follow-up. Complaints remained substantially higher than norm scores for a healthy population. Cortisol after

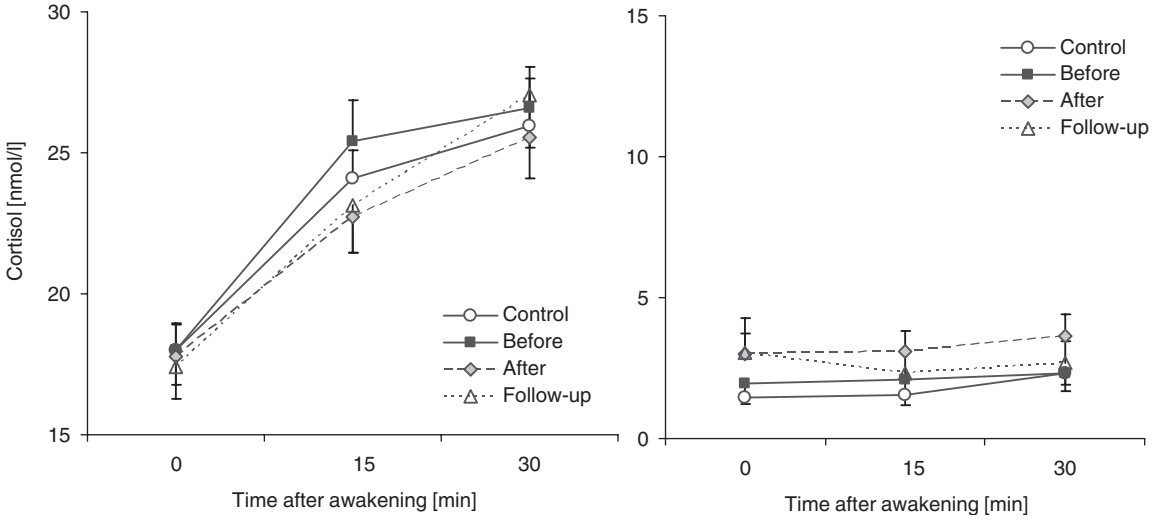

Fig. 1. Cortisol awakening response (CAR, left) and the suppressed CAR after dexamethasone intake (right) in the burnout group before treatment, after treatment and at follow-up, and in the control group. There are no differences between the groups or within the burnout group at consecutive measurements. Means and SEM are shown.

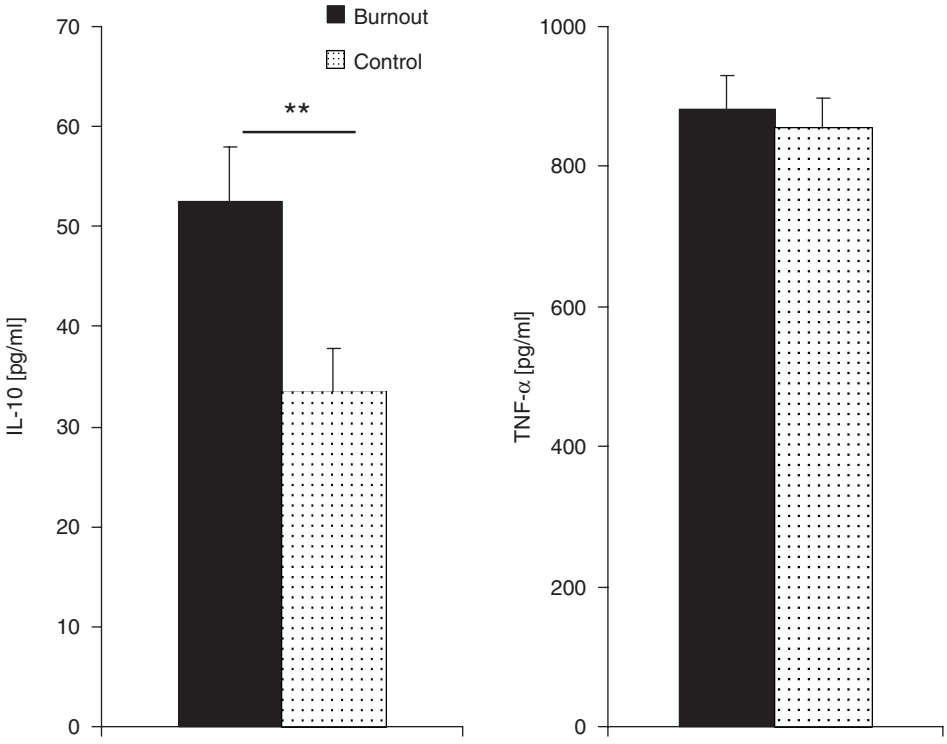

Fig. 2. Anti-inflammatory IL-10 (left) and pro-inflammatory TNF-α release (right) of LPS stimulated monocytes in the burnout and control group. The burnout group had significantly higher levels of stimulated IL-10 ($F_{(1,83)} = 9.01$, $p = 0.004$). Means and SEM are shown.

awakening and after DEX intake (Fig. 1) showed, however, no parallel changes with complaint reduction. Some isolated associations emerged; the CAR (averaged over the three measurements) was significantly correlated with initial exhaustion level. A decrease in depressive symptoms correlated with an *increased* CAR, whereas the decrease in fatigue in time correlated with a *decrease* of the CAR over the three measurements (Mommersteeg et al., 2006). The latter findings are in contradiction to the supposed hyper- and hypoactive state of the HPA-axis in MDD and CFS, respectively, and moreover explained only a minor part of the variance in complaints within (3%) and between (4%) the burnout individuals.

Immune and endocrine variables were studied in another burnout group ($n = 56$) and compared to 38 controls (Mommersteeg et al., 2006). Again no deviations in the cortisol CAR, or in the DEX suppression test (DST) were observed. The dehydroepiandrosterone-sulphate (DHEAS) level (but not the cortisol/DHEAS-ratio) was significantly elevated in the burnout group. The burnout group had significantly higher levels of the anti-inflammatory cytokine IL-10 produced by LPS stimulated monocytes (Fig. 2). The IL-10 production of stimulated T-cells, however, was not different from the control group, and neither were there differences in the pro-inflammatory cytokine release of monocyte TNF-α (Fig. 2) or T-cell IFN-γ. The capacity of DEX to modulate pro- and anti-inflammatory cytokine release in vitro did not differ between the burnout and the control group, nor was there a change in number of whole blood counts of T-cells, B-cells, and NK-cells.

Discussion

The results show that there is no discernable disturbance of salivary cortisol in burnout. There is,

however, an increased production of IL-10 and salivary DHEAS. These findings in a rather large sample of clinical burnout persons raise doubts about the existence of a relevant neuroendocrine dysregulation in burnout as suggested by some earlier studies. Still a variety of (neuroendocrine) factors may show modest disturbances, altogether leading to a state of 'allostatic load' in burnout patients. Though studies in burnout and CFS that included allostatic load parameters do not point in that direction (Cleare, 2003; Grossi et al., 2003; Schnorpfeil et al., 2003), this type of approach may be a viable option for further research.

Another option is that central mechanisms are dysregulated in burnout. To test this possibility the combined DEX/corticotrophin releasing hormone (CRH) test, or CRH or adrenocorticotropic hormone (ACTH) infusion are useful techniques. One may doubt however whether these invasive techniques are acceptable as a research tool for this (relatively) mild syndrome. Our results point toward an increased stimulated monocyte IL-10 release and increased DHEAS levels in burnout. DHEAS has immunostimulatory effects, and at the same time its non-sulphatized form DHEA has been found to reduce susceptibility to viral, bacterial, and protozoan infections (Chen and Parker, 2004). Thus the relevance of the increased DHEAS level in burnout for immune function remains to be determined. Macrophage IL-10 release inhibits T-cell proliferation and suppresses the release of pro-inflammatory cytokines like the anti-viral IFN-γ. People with burnout report more common cold and flu-like infections (Mohren et al., 2003). Moreover, vital exhaustion is related to an increased pathogen burden, with higher IL-10 serum levels (van der Ven et al., 2003). Therefore an increased IL-10 response in burnout may be related to an increased sensitivity for viral infections. Future studies should reveal the relevance of these findings.

When we started this research project we hypothesized that the HPA-axis should show disturbances in burnout. The results showed the absence of any obvious peripheral deviation in salivary cortisol, nor feedback by DEX in burnout. The correlational effects observed in the longitudinal study are too modest to represent any clinical or diagnostic value. Overall we conclude that in this study no obvious disturbance of the HPA-axis in burnout was demonstrated. The possibility of some disturbance in immune function and the hormone DHEAS in burnout deserves further attention, especially in relation to the sensitivity for infections.

Abbreviations

ACTH	adrenocorticotropic hormone
CAR	cortisol awakening response
CFS	chronic fatigue syndrome
CRH	corticotrophin releasing hormone
DEX	dexamethasone
DHEAS	dehydroepiandrosterone-sulphate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Edition IV
DST	dexamethasone suppression test
HPA-axis	hypothalamus pituitary adrenal axis
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IL	interleukin
MDD	major depression disorder
PTSD	post-traumatic stress disorder

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